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Brief Clinical Report

Sutural Exostoses, Rib Hyperostoses, Craniosynostosis, Mental Retardation With Focal Fat Deposition: Proteus Syndrome?

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We report on a 3-year-old boy with cartilaginous exostoses of the cranial sutures, rib hyperostosis, macrocephaly, metopic craniostenosis, epibulbar dermoid, hyperpigmented macules on the neck, focal fat deposition, and mild mental retardation with marked speech delay. Several of these manifestations were reported previously as an "unknown" by Thanos et al. [1977], with additional clinical information and a diagnosis of Proteus syndrome [Cohen, 1993].

KEY WORDS: cranial exostoses, craniostenosis, epibulbar dermoid, hyperostosis, Thanos syndrome, Proteus syndrome

INTRODUCTION

In 1977, Thanos et al. described a single individual with craniostenosis, linear verrucous epidermal nevi, bony cranial exostoses and hyperostosis, epibulbar dermoids, and mental retardation. Subsequently, Cohen [1993] published follow-up clinical information, made a diagnosis of Proteus syndrome and presented the case in support for his causal hypothesis of somatic mosaicism lethal in the non-mosaic state in the pathogenesis of Proteus syndrome.

We report on a child with similar, though not identical manifestations to the case reported by Thanos et al. [1977; Cohen, 1993]. Our patient, like that of Thanos et al. [1977], lacks focal digital overgrowth and connective tissue nevi of the soles of the feet which are considered pathognomonic of Proteus syndrome.

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CLINICAL REPORT

JF was born at term following an uncomplicated pregnancy and normal delivery by Caesarian section. Birth weight was 3.26 kg. Birth length and OFC were not available. Birthmarks were present on the buttocks and neck at birth. He presented at age 6 months with parental concern regarding developmental delay and outgrowths behind both ears and in the occipital area. Clinical evaluation by his family physician confirmed these findings.

Early childhood was characterized by recurrent upper respiratory infections, gradual enlargement of apparent exostoses, the development of pectus excavatum, prominence of the right lower rib cage, and excessive fat deposition over both flanks and the left upper quadrant. There were no significant changes in cutaneous pigmentary findings, and growth was symmetrical.

Psychomotor development remained delayed, with hypotonia. He walked by age 2 years. At 3 years he was clumsy, fell frequently, had poor hand-eye coordination, and his speech was markedly delayed with a few isolated words. Hearing was normal.

At 34 months his weight was 15.8 kg (70th centile), length was 101 cm (90th centile), and OFC was 52.5 cm (97th centile). He has macrocephaly with prominent occiput, mild skull asymmetry, and a square forehead with bifrontal prominences (Fig. 1). Hard nodules were palpable behind each ear, the left greater than the right, resulting in protrusion of the lobules (Fig. 2). A large midline exostosis (1.0 cm diameter) was palpable in the posterior sagittal suture; smaller exostoses (0.5 cm diameter) were palpable in the right coronal suture and left parietal area. There was mild facial asymmetry with prominence of the left temporal area and ear, metopic ridging, prominent glabella, hypertelorism (3.4 cm, >97th centile), high nasal bridge, flare of the nasal cartilage, downslanting palpebral fissures (right greater than left), ectropion of the right lower lid, and epibulbar dermoid of the right conjunctiva (Fig. 3). There was downslant of the corners of the mouth, normal palate, notching of his left upper central incisor, maloccluded teeth, and enamel hypoplasia. Pec-

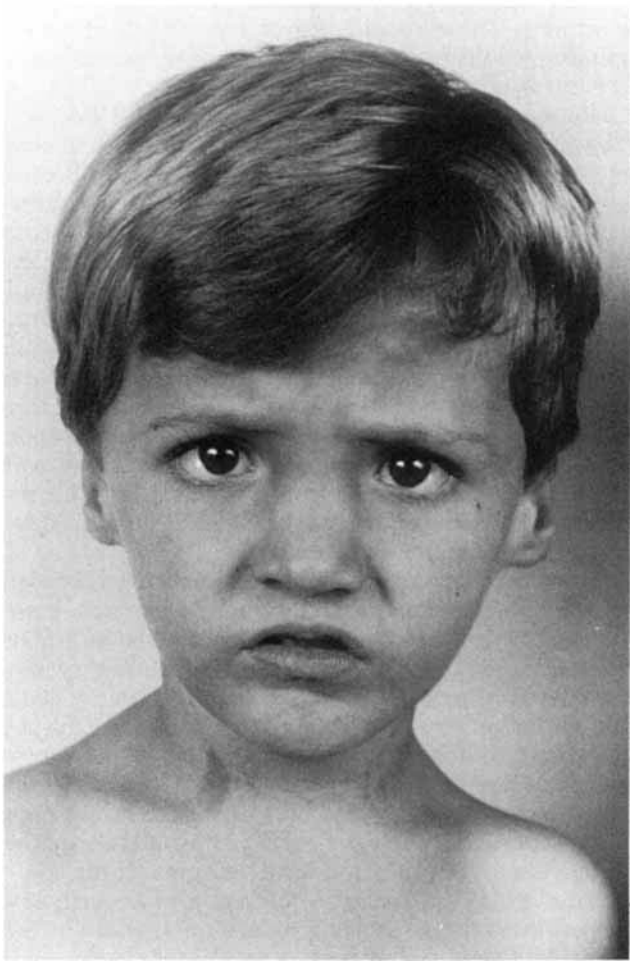

Fig. 1. Face of patient. Note broad forehead, protrusion of the left ear, mild facial asymmetry, prominent glabella, high nasal bridge, flaring of the nasal cartilage, down slanting palpebral fissures and corners of the mouth, ectropion of the right lower eyelid, and hyperpigmented macules in the neck.

tus excavatum with Harrison's sulci, and posterior prominence of the 10th ribs was present (Fig. 4). The abdomen was protruding with excessive fat deposition most markedly over the left upper quadrant and

Fig. 2. Left ear of patient. Note nodules behind ear.

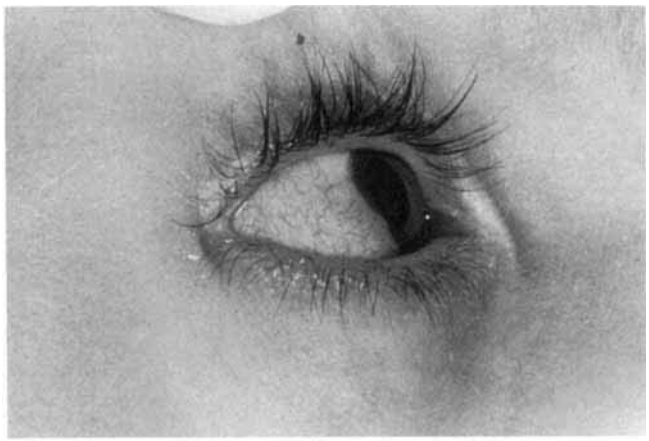

Fig. 3. Right eye of patient. Note epibulbar dermoid.

both flanks, and minimal fat deposition of the limbs. Musculoskeletal anomalies include narrow shoulders, small scapulae with winging, mild cutaneous webbing of the fingers, mild camptoclinodactyly of the fifth fingers, and no kyphoscoliosis. Cutaneous abnormalities included irregular linear hyperpigmented macules bilaterally on the neck (Fig. 1) and a port wine stain on left buttock (5.0 × 2.7 cm). CNS examination was without focal abnormalities.

Griffith's Scale of Mental Assessment indicated a general quotient of 60.9 (mild mental retardation). The speech development subquotient was the most markedly delayed.

Diagnostic investigations showed karyotype was normal, 46,XY. Tomography of the skull demonstrates the presence of a cartilaginous exostosis, without calcium deposition, arising from the posterior sagittal suture

Fig. 4. Back of patient. Note prominence of the 10th ribs, most marked on the right.

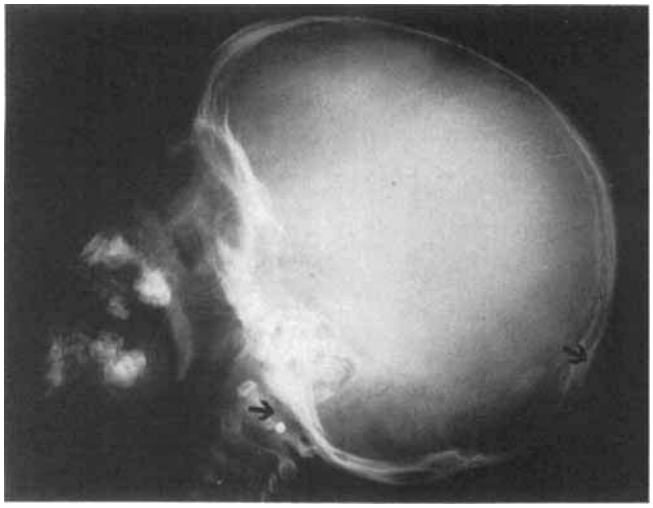

Fig. 5. Left lateral skull roentgenogram. Arrows indicate position of exostoses. Note inward denting of skull in parietal area.

(Fig. 5). CT scan of the brain and orbits was interpreted as normal. Hyperostosis of the 10th ribs, right greater than left, are present on skeletal survey. There were no long bone exostoses. Magnetic resonance imaging of the abdomen to evaluate a possible tumour identified homogeneous fat deposition in both flanks and in the left upper quadrant (Fig. 6).

DISCUSSION

The clinical findings of multiple cartilaginous cranial exostoses confined to sutural sites, rib hyperostosis, abnormal fat deposition, café-au-lait maculas, epibulbar dermoid, minor facial anomalies, developmental delay, and the other manifestations seen in JF are to our knowledge unique. However, they overlap those reported by Thanos et al. [1977; Cohen 1993] in that both patients had craniostenosis, craniofacial asymmetry, hypertelorism, flaring of the nasal cartilage, epibulbar dermoids, and developmental delay. Our patient lacked the bony nasal exostoses and linear verrucous epidermal nevus reported in the Thanos case [1977]. Neither patient had digital overgrowth or planter hyperkeratosis. Cohen [1993] considered the diagnosis in the patient reported by Thanos et al. [1977] to be Proteus syndrome. The clinical features reported in JF, in our opinion, would represent an unusual presentation for Proteus syndrome.

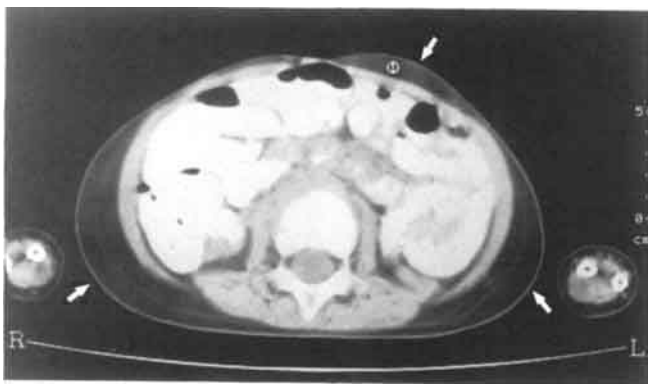

Fig. 6. MRI scan of abdomen. Fat deposition in flanks and left upper quadrant indicated by arrows.

Named after the mythical Greek god Proteus, a "shape-changer," this syndrome is as difficult to characterize as its namesake. The characteristics of Proteus syndrome include a) overgrowth, in particular hemihypertrophy and macrodactyly of fingers or toes; b) cutaneous manifestations, in particular hyperkeratotic, hyperpigmented nevi; and c) tumours, most commonly lipomata on the trunk, buttocks and thighs, and hamartomata with lymphatic, fatty, and/or hemangiomatous elements. Associated abnormalities are common, including bony exostoses of the skull, macrocephaly without brain malformations, and scoliosis. Stature is usually normal; however, generalized overgrowth has been reported. Developmental delay is present in 55% of reported cases [Clark et al., 1987; Viljoen et al., 1987; Gorlin et al., 1990].

Embryogenesis and growth are complicated developmental processes, controlled by multiple genes. Regulation of body form and maintenance of body proportions is inadequately understood. Proteus syndrome most likely represents a family of disorders in which there is loss of regulation of histogenesis. One can speculate that Knudson's hypothesis applies to focal body overgrowth as it does for embryonic tumours. A gene mutation requires a second hit to result in loss of regulation of body form in focal areas. Alternative hypotheses for the pathogenesis of focal overgrowth include, a somatic mutation, lethal in the nonmosaic state, or a paracrine disorder resulting in local production or regulation of tissue growth factors resulting in overgrowth [Kousseff, 1992; Cohen, 1993].

Distortion of body structure, plantar hyperkeratosis, macrodactyly, and lipomata, in particular, is what makes Proteus syndrome unique from other disorders with focal overgrowth. Overlap of Proteus syndrome with neurofibromatosis, Klippel-Trenauney-Weber, encephalocutaneouslipomatosis (ECCL), and Maffucci syndromes is present. Similarly, our patient JF and the one reported by Thanos et al. [1977] have a similar condition. However, just as the presence of a café-au-lait macule does not permit a diagnosis of neurofibromatosis, nor a haemangiomata of the buttock imply a diagnosis of Klippel-Trenauney-Weber, the presence of abnormal fat deposition in the flanks of JF may not imply a diagnosis of Proteus syndrome. Presently, it is unclear if JF will develop pathopneumonic signs of Proteus syndrome or if the manifestations in this child will have a different prognosis. Thus, ongoing monitoring is indicated for this child, and similar patients, because of the concern of tumours and complications of focal overgrowth.

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